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(71) Applicant *(for all designated States except US)*: US BIOMATERIALS CORPORATION [US/US]; One Progress Boulevard, Box #23, Alachua, FL 32615 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LATORRE, Guy [US/US]; 4416 N.W. 60th Terrace, Gainesville, FL 32606 (US). LEE, Sean [US/US]; 737 N.W. 84th Street, Gainesville, FL 32607 (US). ZHONG, Jipin [CN/US]; 3636 N.W. 68th Lane, Gainesville, FL 32653 (US). FOSMOE, Al [US/US]; 2111 S.W. 122nd Street, Gainesville, FL 32607 (US).

(74) Agents: BAUM, Allen, R. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US).

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(54) Title: BIOLOGICALLY ACTIVE GLASS-BASED SUBSTRATE

(57) Abstract

Compositions including a glass composition and a biodegradable polymer, and methods of preparation and use thereof for growing tissue, including bone, are disclosed. The glass is formed from oxides of silicon, phosphorus, sodium, and calcium, and is dispersed within a porous biodegradable polymer to form a three dimensional matrix. The compositions can be in any suitable form for administration to a patient, such as sheets, screws, stents, pins, sutures, prosthetics, valves, plates and the like, or can be in a form suitable for use in *in vitro* applications.

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BIOLOGICALLY ACTIVE GLASS-BASED SUBSTRATE

FIELD OF THE INVENTION

The present application relates to porous materials that can be used as three dimensional substrates on which to grow certain cell lines in culture and to the use of such substrates in medical practice.

BACKGROUND OF THE INVENTION

In many tissue engineering methods, a population of viable cultured cells are seeded into a porous, solid, biodegradable substrate. As the cells grow into and throughout this three-dimensional substrate, they lay down the extracellular matrix proteins and other molecules which eventually become a solid tissue implant material. The original substrate material will eventually be totally resorbed, either at the time of implant or sometime thereafter, so that only the generated extracellular matrix (and if desired, the cells) will remain.

One example of a tissue culture matrix is where dermal fibroblasts are cultured in a polyglycolic acid (P G A) sponge to grow a collagen dermal equivalent for implants onto the skin, e.g., DermaGraft^{TM} dermal implant material (supplied by Advanced Tissue Sciences). Chondrocytes may be cultured into the same material to produce artificial articular cartilage.

The desirable characteristics for a tissue growth substrate are that it (1) be resorbable within an appropriate time frame, (2) provide a desirable chemical environment for cell attachment, growth and/or activity, (3) have appropriate pore structure and/or surface texture for cell infiltration and (4) act as a suitable contact guidance system for cell migration and extracellular matrix deposition.

One significant disadvantage of an acidic polymer such as a polylactic acid/polyglycolic acid (P L A/P G A) growth substrate, is that it lowers the pH of the medium substantially as it degrades, thereby inhibiting cell growth and activity. Allogeneic/xenogeneic collagen sponge substrates are sometimes used as well, however, there are difficulties associated with disease transmission, potential host immunological response, handling and mechanical properties as well as cellular interactions.

Bioglass® is a biologically active synthetic material that includes varying compositions of SiO_2 , P_2O_5, CaO, and Na_2O (*e.g.* see L.L. Hench, *et al.*, "Biological Applications of Bioactive Glasses," *Life Chemistry Reports*, 13, 187-241 (1996) and L.L. Hench, *et al*, Ed.s, *An Introduction to Bioceramics*, World Scientific, New York (1993)), has been shown in numerous *in vitro* and *in vivo* studies to be a bio-compatible surface for cell growth and activity. Bioglass® interacts with the host environment by a series of chemical reactions involving ion exchange and precipitation of mineral layers onto the surface. Melt-derived Bioglass® particles by themselves have been shown *in vitro* to raise the pH of the medium depending on composition and particle size. Sol-gel derived Bioglass® particles and fibers by contrast, contain no sodium and do not increase the pH of the host medium as it reacts as significantly as melt-derived Bioglass® particles. Similarly, melt-derived Bioglass® which has been pre-reacted in buffer solution for a specified amount of time may also maintain a more stable pH environment.

There is a need for biologically active glass-based substrates which are chemically, physically, and mechanically stable and which can be formed into semi rigid shapes to serve as substrates for tissue growth with controllable change in pH at the site of tissue growth. The present invention provides such materials.

SUMMARY OF THE INVENTION

Compositions useful for growing tissue, including bone, and methods of preparation and use thereof, are disclosed. In one embodiment, the composition includes a biologically active material formed from oxides of silicon, phosphorus, sodium, and calcium, dispersed within a biodegradable polymer sponge material to form a three dimensional matrix. In a second embodiment, the composition includes porous meshes that include spun fibers of a biologically active material that includes oxides of silicon, phosphorus, sodium, and calcium to form a three dimensional matrix. In a third embodiment, the composition includes porous ceramic materials produced by sintering a biologically active glass powder, either as a sol-gel, melt-derived or pre-reacted melt derived form. This sintered material forms a porous three-dimensional matrix, which maintains a controllable pH as it reacts in the environment. The porous materials described herein are ideally suited for applications such as tissue engineering which benefit from a high degree of porosity.

The polymer matrix includes biodegradable polymeric materials. Suitable biodegradable polymers include polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polysaccharides, proteins, polyanhydrides, polyphosphazenes, and copolymers and blends thereof.

The percent by weight of the glass composition to polymer is between 5 and 95%. The porosity of the glass is between 0 and 85%. The composition and any articles of manufacture that include the composition may or not be porous, and preferably has an overall porosity between about 0 and 80%.

The compositions can optionally include additional components, such as non-degradable polymers, various biologically active substances such as growth factors (including TGF-β, basic fibroblast growth factor (bFGF), epithelial growth factor (EGF), transforming growth factors α and β (TGF α and β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor/vascular permability factor (VEGF/VPF)), antivirals, antibacterials, antiinflammatories, immunosuppressants, analgesics, vascularizing agents, cell adhesion molecules (CAM's), bone morphologenic proteins (BMP's) and anticoagulants.

The compositions can be in any suitable form for administration to a patient, such as sheets, screws, stents, pins, sutures, prosthetics, valves, plates, tubes and the like, or may be moldable or machinable.

The compositions can be used as substrates to promote the growth of tissue, including bone, *in vitro*, *ex vivo* and/or *in vivo*.

DETAILED DESCRIPTION OF THE INVENTION

Compositions useful for growing tissue, including bone, and methods of preparation and use thereof, are disclosed. In one embodiment, the composition includes a biologically active material formed from oxides of silicon, phosphorus, sodium, and calcium, dispersed within a biodegradable polymer sponge material to form a three dimensional matrix. In a second embodiment, the composition includes porous meshes that include spun fibers of a biologically active material that includes oxides of silicon, phosphorus, sodium, and calcium to form a three dimensional matrix. In a third embodiment, the composition includes porous ceramic materials produced by sintering a biologically active glass powder, either as a sol-gel or pre-reacted melt derived form. This sintered material forms a porous three-dimensional

matrix, which may be tailored to maintain a desirable pH as it reacts in the environment of use.

These compositions are superior to prior bioactive compositions used in cell culture. For example, the use of bioactive glass alone does not provide for the superior structure obtainable when the combination of bioactive glass and a biodegradable polymer are used to provide a three dimensional cell culture media. Further, the use of polymers in the composition allows for a greater range of available structures.

Definitions

The following definitions are used herein:

The term "biodegradable" as used herein refers to any material that is capable of being decomposed by natural biological processes, including those occurring *in vivo* or *in vitro*.

The term "bioactive glass" as used herein refers to any glass composition capable of eliciting a specific biological response at the interface of the material which results in the formation of a bond between the tissue and the material. This typically includes any bioactive glass composite material that includes, at least, silicon oxide, phosphorus oxide, calcium oxide and sodium oxide, in various proportions.

The term "three dimensional matrix suitable for cell growth" as used herein is intended to mean any porous structure comprising a bioactive glass dispersed within a biodegradable polymer capable of culturing cells. The three dimensional matrix may, in some applications, be implanted into a patient. In other applications,

the three dimensional matrix may be used only as an *ex vivo* platform for cell growth.

I. Composition

A. Composition of the Glass

The glass preferably includes between 40 and 86% by weight of silicon dioxide oxide (SiO_2), between about 0 and 30% by weight of sodium oxide (Na_2O), between about 4 and 46% by weight calcium oxide (CaO), and between about 1 and 15% by weight phosphorus oxide (P_2O5). More preferably, the glass includes between 40 and 60% by weight of silicon dioxide oxide (SiO_2), between about 5-30% by weight of sodium oxide (Na_2O), between about 10 and 35% by weight calcium oxide (CaO), and between about 1 and 12% by weight phosphorus oxide (P_2O5). The oxides can be present as solid solutions or mixed oxides, or as mixtures of oxides.

CaF_2, B_2O_3, Al_2O_3, MgO and K_2O may be included in the composition in addition to silicon, sodium, phosphorus and calcium oxides.

The glass is preferably present as a porous material. The pore size is between about 0 and 500 μm, preferably between about 10 and 150 μm, and more preferably, between about 50 and 100 μm. The degree of porosity of the glass is between about 0 and 85 %, preferably between about 30 and 80 %, and more preferably, between about 40 and 60 %.

The most preferred glass is Bioglass®™ (a trademark of University of Florida), which has a composition including about 45% by weight silicon dioxide, about 24.5% by weight sodium oxide, about 6% by weight phosphorus oxide, and about 24.5% by weight calcium oxide. Another preferred material is hydroxyapatite.

Biologically active glass-based substrates for tissue engineering are advantageous because they apparently readily incorporate and promote the production of collagen and other extracellular matrix proteins *in vitro* and *in vivo*, although the exact mechanism for this effect is not yet known.

B. Biodegradable Polymers

The polymer matrix includes biodegradable polymeric materials. Suitable biodegradable polymers include polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polycarbonates, polyorthoesters, polysaccharides, proteins, polyanhydrides, polyphosphazenes, and copolymers and blends thereof.

The selection of the biodegradable polymer depends on several factors, including the desired degradation time, the physical properties, including melting temperature and hardness, and chemical properties (i.e., the interaction of the polymeric materials with other components in the composition). Preferred polymers include polylactic acid, polyglycolic acid, and copolymers and blends thereof.

It is particularly desirable, when using a polyanhydride or polyester, which degrade to acidic components, to have a sufficient quantity of the glass such that the co-degradation of the glass and polymer provide a somewhat buffered system, since the metal oxides, when reacted with water, produce a "basic" metal hydroxide. The combination of glass and polymer can provide a reasonably stable pH for use as a tissue culture matrix.

Biodegradable polymers such as those described above are well known to those of skill in the art, and can be prepared using known methodology. Suitable biodegradable polymers are described, at least, in U.S. Patent No. 4,080,969 to Casey et al., U.S. Patent No. 4,194,066 to Kaetsu et al., and U.S. Patent No. 5,410,016 to Hubbell et al.

The polymer preferably includes carboxylic acid functional groups, or includes anhydride or ester bonds which, upon hydrolysis, provide carboxylic acid functional groups. These groups assist in adhesion of cells to the polymer, which is desirable in a composition used for cell culture. Further, cell adhesion peptides, such as arginine-glycine-aspartic acid (RGD) can be incorporated into the polymer matrix or covalently linked to the polymers to assist with adhesion of cells to the polymer matrix.

The polymer is preferably present as a porous material, i.e., a porous polymer foam. The pore size is between about 0 and 1,000 μm, preferably between about 100 and 800 μm, and more preferably, between about 200 and 500 μm. The degree of porosity of the polymer is between about 0 and 85 %, preferably between about 30 and 80 %, and more preferably, between about 40 and 60 %.

The higher the degree of porosity, the higher the seeding of cells into the matrix and the better able these cells are to receive nutrients from the surrounding medium. However, increased porosity can lead to decreased dimensional stability. Those of skill in the art can select an appropriate porosity taking into consideration the type of cells to be seeded, and the requisite dimensional stability of the composition. The dimensional stability requirements are a function of how the composition will be used. If the composition is to be used as a three dimensional *in vitro* cell culture or a tissue engineering platform, the mechanical properties (e.g. Young's modulus) are not as critical as those required for an *in vivo* implant device.

C. Optional Components

The compositions can optionally include additional components, such as non-degradable polymers, various biologically active substances, and structural components.

Non-degradable polymers are preferably those that do not cause a non-desirable effect when implanted in vivo. Suitable non-degradable polymers include polyacrylates such as polymethyl methacrylate (PMMA), polysulfones, polystyrene, polyalkylene oxides such as polyethylene oxide and polyethylene oxide/polypropylene oxide copolymers (Pluronics™), polyvinyl alcohol, polyolefins such as polypropylene and polyethylene, polytetrafluoroethylene (Teflon™).

Suitable biologically active substances specifically include those which promote healing and regulate cell/tissue growth, including bone growth. Such substances include, but are not limited to, growth factors (including TGF-β, basic fibroblast growth factor (bFGF), epithelial growth factor (EGF), transforming growth factors α and β (TGF α and β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor/vascular permability factor (VEGF/VPF)), antivirals, antibacterials, antiinflammatories, immunosuppressants, analgesics, vascularizing agents, cell adhesion molecules (CAM's), bone morphologenic proteins (BMP's), anticoagulants, nutrients, antivirals, antibacterials, antiinflammatories, immunosuppressants, and analgesics.

Additional components can be added to increase the structural integrity of the composition. These include metals, ceramics, and other materials. In one embodiment, the composition includes a shape-memory polymer or metal alloy, such as TiNi, such that the composition can flex and return to its original position while bone or other cells/tissues are growing into the composition.

D. Cells and Tissue Types Which can be Used with the Composition

The composition can be used to grow several different types of tissue. Bone tissue can be grown by seeding cells such as osteoprogenitor cells, bone marrow cell preparations, cells of osteoblastic phenotypic potential or of osteoblastic phenotypes.

The matrix prepared from the composition can also be seeded, for example, with fibroblasts and chondrocytes. Preferably, the matrix is seeded with cells from the patient to be treated to avoid problems associated with tissue rejection. Less preferably, the cells are isolated from another human or from an animal source suitable for xenotransplantation into a human.

The cell seeding density is a function of the cell type being cultured. For most cells, typical cell densities range from between about 10^5 and 10^6 cells per cm^3. For example, chondrocytes are typically seeded at a density of about 4×10^5 cells per cm^3.

Suitable cell types that can be seeded include adipose cells, epithelial cells, endothelial cells, hepatocytes, smooth muscle cells, neurons, osteoclasts, chondrocytes, skin cells, mesenchymal cells, islet cells, keratinocytes, blood cells, mast cells, myocytes, stem cells and T cells.

E. Composite Material Prepared from the Glass and the Polymer

The glass and polymer are combined to form a composite material that include both the glass and polymeric elements and which also optionally includes cells and other bioactive materials such that the composite can be used to grow cells and tissue, including bone tissue. The pores of the composite material can be controlled in manufacturing to yield desirable size ranges for cell migration, such as

between about 5 and 25 μm to enhance cell migration, and between about 400 and 500 μm to accomodate ingrowth of a cappilary bed system. Preferably, the material is not flat, but rather, is three dimensional, to allow for cell growth.

The composite material is preferably arranged in a manner which mimics the fiber density and orientation of the target tissue, yielding an implant whose mechanical properties match those of the surrounding tissue.

The composite material preferably includes melt-derived biologically active glass particles, such as Bioglass® (trademark of University of Florida), and PLA, PGA or copolymers and blends thereof. The composite material is fully resorbable over time, with a resorption rate depending on the exact composition of the material. Because melt-derived Bioglass® tends to raise the pH of the medium as it reacts, this tends to buffer the pH change from the polymer degradation. The buffering effect as well as the total degradation time depend upon the relative amounts of, and composition of, both the polymer and glass particulate in the material, as well as the pore texture of the composite material. By controlling the composition and porosity of the glass composition, the rate of degradation, effect of the composition on the surrounding pH and the corresponding ion release rate can be controlled. Those of skill in the art can readily optimize the composition to allow for optimal cell migration, activity, degradation time and final growth of the artificial tissue at a stable pH.

In another embodiment, the glass is in the form of spun fibers of Sol-gel derived or melt-derived Bioglass®. These fibers may be conglomerated in some fashion to yield a network with an average spacing between fibers equal to the target pore size for cell migration and matrix deposition. In this embodiment, the fibers can, but need not, include a biodegradable polymer.

In yet another embodiment, the glass is in the form of sintered glass particles, preferably sintered particles of bioactive glass. The particles may be in sol-gel derived, or pre-reacted melt derived form.

F. Articles of Manufacture Prepared from the Composition

The compositions can be used for several purposes, including *in vitro* and *ex vivo* production of cells and tissue, including bone tissue, or for *in vivo* uses. For *in vitro* use,
the material is preferably in the form of a sheet, a foam, or other shape suitable for tissue culture *in vitro*. Preferably, the material is not flat, but rather, is three dimensional, to allow for cell growth. The material can be shaped to fit a particular defect, for example a bone defect, thus allowing bone or other tissue to grow through the material and fill the defect.

For *in vivo* use, the composition can be used to correct a bone defect, or otherwise implanted where tissue growth, including bone growth, is desirable. For this embodiment, suitable forms for the composition include sheets, screws, stents, pins, sutures, prosthetics, valves, plates, tubes and the like.

II. Methods of Manufacturing the Glass Composition

The glass composition can be prepared in several ways, to provide melt-derived glass, spun fibers of sol-gel derived glass, and sintered glass particles. The sintered particles may be in sol-gel derived, or pre-reacted melt derived form. Sol-gel derived glass is generally prepared by synthesizing an inorganic network by mixing metal alkoxides in solution, followed by hydrolysis, gelation, and low temperature (600-900°C) firing to produce a glass. Melt derived glass is generally prepared by mixing grains of oxides or carbonates, melting and homogenizing the

mixtures at high temperatures, typically between about 1250 and 1400°C. The molten glass can be fritted and milled to produce a powder or casted into steel or graphite molds to make bulk implants.

The glass composition is preferably melt-derived. In each preparation, it is preferred to use reagent grade glass, especially since the glass is used to prepare materials which ultimately may be implanted in a human.

A. Melt Derived Glass

A melt-derived glass composition can be prepared, for example, by preparing an admixture of the individual metal oxides and other components used to prepare the glass composition, blending the admixture, melting the admixture, and cooling the mixture. The melting temperature is determined in large part by the glass composition, and ranges, for example, from about 900-1500°C, preferably between about 1250 and 1450°C. The melt is preferably mixed, for example, by oxygen bubbling, to ensure a thorough homogenation of the individual components.

The mixture can be cooled, for example, by adding the molten admixture to a suitable liquid, such as deionized water, to produce a glass frit. Porosity can be introduced by grinding the glass into a powder, admixing the powder with a foaming agent, and hot pressing the mixture under vacuum and elevated temperature. The particle size of the glass powder is between about 40 and 70 μm, the vacuum is preferably less than 50 MPa, and the hot pressing is preferably performed at a temperature above 400°C, preferably between about 400 and 500°C. Suitable foaming agents include compounds which evolve carbon dioxide and/or water at elevated temperatures, for example, metal hydroxides, metal carbonates, and peroxides, such as hydrogen peroxide. Preferred metal carbonates are sodium bicarbonate, sodium carbonate and calcium carbonate. The foaming agents are

preferably added in a range of between about 1-5, more preferably 2-3 percent by weight of the glass powder. The preparation of melt-derived porous glass is described, for example, in U.S. Patent No. 5,648,301 to Ducheyne and El Ghannam, the contents of which are hereby incorporated by reference.

B. Sintered Glass Particles

Glass can be sintered using known methodology. In one embodiment, an aqueous slurry of the glass powder and a foaming agent with a suitable binder, such as polyvinyl alcohol, is formed. The slurry is then poured into a mold, allowed to dry, and sintered at high temperatures. These temperature may range, depending on the glass composition and foaming agent used, between about 500 and 1000°C, more preferably between about 600 and 800°C.

C. Spun Fibers of Sol-gel Derived Glass

It is known in the art to control the heat treatment cycle of glass gels to control the pores and interpores of the material to create a porous glass material. However, since a pore diameter larger than 0.1 microns is difficult to achieve using this method, the sintering and foaming processes described herein are generally more preferred.

D. Leaching of the Porous Material

To aid in preparing glass compositions with high porosity, the glass composition can include a material which can be preferably leached out of the glass composition, and, in doing so, provide the composition with high porosity. For example, minute particles of a material capable of being dissolved in a suitable solvent, acid, or base can be mixed with or melted into the glass, and subsequently

leached out. The resulting voids have roughly the same size as the particle that was leached out. In the case of a material which is part of a melt-derived glass composition, the size of the pores and degree of porosity depends on the amount of added material relative to the amount of glass. For example, if the leached material constituted about 80% of the glass, then the glass would be approximately 80% porous when the material was leached out. When leaching the glass composition, care should be taken not to leach out those components which add to the bioactivity of the glass, i.e., the calcium and phosphorus oxides.

E. Optional Treatment of the Resulting Porous Glass Material

In some embodiments, the surface of the glass composition, being relatively acidic (due to Si-O-H bonds), may need to be neutralized to maximize compatibility with the cells to be seeded on the resulting matrix. This can be accomplished, for example, by contacting the glass composition with a suitable buffer for a suitable amount of time to neutralize the surface of the glass (including the surfaces of the voids and pores). Suitable buffers are well known to those of skill in the art, and include TRIS, HEPES, and phosphate buffered saline. Preferably the buffer solution is isotonic with the inside of the cells being cultured on the resulting matrix.

In one embodiment, the glass composition is contacted with cell adhesion peptides, such as RGD, and/or other materials, such as fibronectin, to provide for improved adhesion of the cells to be cultured to the glass composition.

III. Methods of Manufacturing the Polymer-Glass Composite Matrix

Polymer matrices including the glass composition can be prepared, for example, by melting the polymer, adding the glass composition and any optional components, and cooling the polymer. To provide porosity, blowing agents such as carbon dioxide or low boiling organic solvents, such as freon, can be used. Optionally, components such as salts and sugars which can be readily leached away from most biodegradable polymers, can be added and leached out to provide porosity. However, care must be taken that the leaching of these materials does not adversely leach out too much of the polymer, particularly when water sensitive polymers such as polyanhydrides are used.

Another method for preparing the polymer-glass matrix is to dissolve the polymer in a suitable solvent, add the glass composition and any optional components, and then add a non-solvent for the polymer to cause the polymer to precipitate. Performing the precipitation while simultaneously introducing a foaming agent, for example a gas such as carbon dioxide, will cause the polymer to precipitate as a foam or sponge which includes the glass composition dispersed therein.

IV. Methods for Shaping the Polymer-Glass Composite Matrix

The composite can be shaped at the same time it is being prepared, for example, by melting the polymer, adding the glass and any optional components, pouring the melt into a suitable mold, and cooling the mixture. When a leaching process is used to increase the porosity of the composite matrix, it is preferable that the mold include holes which allow the solvent to pass through the mold.

The composite can also be shaped as it is formed using three dimensional printing techniques. In this embodiment, it may be preferable that the polymer include reactive functional groups, such as olefins (preferably in the form of acrylate groups), which can be used to adhere a printed layer to a subsequent printed layer by reacting the groups between the two layers.

The composite can be shaped after it is prepared using conventional techniques, such as laser ablation, extrusion, milling, cutting, and computer aided design/computer aided manufacture (CAD/CAM) techniques.

V. Methods of Using the Composite Matrix

The composite matrix can be used as a substrate to promote the growth of tissue, including bone. When used *in vitro*, the matrix is optionally washed with a buffer solution, optionally contacted with cell adhesion peptides or other cell adhesion promoting compounds, and seeded with cells and/or tissue. The matrix is kept in a suitable medium, for example, minimum essential medium, provided with suitable nutrients, and the cells are allowed to grow. The cells and/or tissue can be harvested after the desirable growth is obtained. The harvested cells and/or tissue can be used for implantation, by themselves or while still incorporated in the matrix.

The biologically active glass-based substrates are advantageous for use in tissue engineering because collagen fibers have been seen *in vitro* and *in vivo* to bond strongly to and be embedded into biologically active glass. This strengthens and promotes the growth of collagen-rich tissues.

There are several *in vivo* uses for the composite matrix to grow artificial tissues. For example, if dermal fibroblasts are cultured in a suitable substrate, they

lay down collagen and other extracellular matrix proteins to form a dermal layer which may then be implanted onto an injured host site. Chondrocytes cultured in a similar way can produce a cartilage implant material.

When used *in vivo*, the matrix is optionally washed with a buffer solution, optionally contacted with cell adhesion peptides or other cell adhesion promoting compounds, and implanted to a desired site in a patient. Since the individual components in the matrix are substantially biodegradable and/or biocompatible, the matrix does not need to be removed following implantation.

The following non-limiting examples are submitted to demonstrate the preparation of composition of the present invention. These examples are not intended to limit the scope of the invention in any way.

EXAMPLES

Example 1. Bioglass® /PGA/PLA Composite

PLA, PGA and copolymers and blends thereof are dissolved in a suitable solvent, *e.g.*, acetone, methylene chloride or chloroform, and precipitated from solution with a non-solvent for the polymer *e.g.*, ethanol, methanol, diethyl ether, or water. The remaining solvent and non-solvent are removed, for example, by extraction, evaporation, centrifugation, or other means, to provide a coherent polymeric mass. The mass is subsequently shaped. If there are reactive groups on the polymer, these are then cured. Dry Bioglass® powder is added at various stages during this process, preferably in the range of 10 to 40 volume percent, to yield the desired composite material.

Example 2. Bioglass® fibers from Sol-gel

Sol-gel Bioglass® is produced as a precipitate from TEOS, phosphorous alkoxide and calcium nitrate in water-ethanol. Continuous fibers are prepared by extruding the sol through a spinneret. The fibers are then aged, dried, and thermally stabilized. Long fibers may be woven into a mesh, short fibers may be combined by mixing them with a degradable adhesive, such as a solution of carboxymethylcellulose (CMC). The resulting material is then heated in a kiln to sinter the material and burn off the binder. The sintered structure may then be impregnated with a bioresorbable (biodegradable) polymer.

Example 3. Sintered Bioglass®

Sol-gel derived Bioglass® powder is mixed with a solution of CMC to form a viscous paste. This paste is then allowed to dry, and the CMC polymer is allowed to cross-link. The resulting dry, hardened material is then heated in a kiln to sinter the material. The resulting macroporous structure can then be impregnated, for example by vacuum impregnation methods, with a biodegradable polymer to form a composite substrate.

We claim:

1. A composition comprising a biodegradable polymer with a bioactive glass dispersed therein, wherein the glass comprises SiO_2, Na_2O, CaO, and P_2O_5, and wherein the combination of said polymer and said glass provides a three dimensional matrix suitable for cell growth.

2. The composition of claim 1 wherein the glass includes between about 40 and 86 percent by weight of SiO_2, between about 0 and 30 percent by weight of Na_2O, between about 4 and 46 percent by weight of CaO and between about 1 and 15 percent by weight of P_2O_5.

3. The composition of claim 1 wherein the overall composition has a porosity of between about 0 and 80%.

4. The composition of claim 1 wherein the biodegradable polymer is a polyhydroxy acid, polyorthoester, polylactone, polycarbonate, polysaccharide, protein, polyanhydride, polyphosphazene, copolymer thereof or blend thereof.

5. The composition of claim 4 wherein the polyhydroxy acids are polylactic acid, polyglycolic acid, copolymers thereof or blends thereof.

6. The composition of claim 1 wherein the ratio by weight of glass to polymer is between about 5 and 95%.

7. The composition of claim 1, further comprising a biologically active substance, wherein the substance is a growth factor, cell adhesion molecule, bone morphogenic protein, nutrient, antiviral, antibacterial, antiinflammatory, immunosuppressant, analgesic, vascularizing agent, anticoagulant or mixture thereof.

8. The composition of claim 1, wherein the glass composition is in the form of a melt-derived glass.

9. The composition of claim 1, wherein the glass composition is in the form of a sol-gel derived composition.

10. The composition of claim 1, wherein the glass composition is in the form of a sintered glass derived composition.

11. The composition of claim 1, wherein the glass composition is in the form of spun fibers.

12. The composition of claim 1, wherein the composition is in the form of sheets, screws, stents, pins, sutures, prosthetics, valves, tubes or plates.

13. The composition of claim 1, further comprising cells.

14. The composition of claim 13, wherein the cells are selected from the group consisting of fibroblasts and chondrocytes.

15. A method for culturing cells *in vitro* comprising seeding cells in a matrix comprising a biodegradable polymer with a bioactive glass dispersed therein.

16. A porous polymer matrix comprising:

a) a biodegradable polymer and

b) a bioactive glass dispersed therein,

wherein the porosity of the matrix is sufficient to promote cell growth *in vitro*.

17. The matrix of claim 16, wherein the porosity is between about 30 and 80%.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16470

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C08K 3/00, 3/20, 3/22
US CL :524/847
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 524/847

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,744,515 A (CLAPPER) 28 April 1998, col. 7, line 56, to col. 8, line 27.	1-17
A	US 5,567,612 A (VACANTI et AL) 22 October 1996, see entire document.	1-17
A	US 5,525,646 A (LUNDGREN et al) 11 June 1996, see entire document.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer NATHAN M. NUTTER Telephone No. (703) 308-0661

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